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Atty. Dkt. No. NB 2004.02 (060925-0402)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: H. Michael SHEPARD et al.

Title: ENZYME CATALYZED  
THERAPEUTIC AGENTS

Appl. No.: 09/782,721

Filing Date: 2/12/2001

Examiner: Crane, Lawrence E.

Art Unit: 1623

<p><b>CERTIFICATE OF MAILING</b></p> <p>I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below.</p> <p><u>Mary R. Zimmerman</u> (Printed Name)</p> <p><u>[Signature]</u> (Signature)</p> <p><u>April 14, 2006</u> (Date of Deposit)</p>
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**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Mail Stop Amendment  
Commissioner for Patents  
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Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

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**TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of either a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

**RELEVANCE OF EACH DOCUMENT**

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

**FEE**

A check in the amount of \$180.00 is enclosed in accordance with 37 CFR §1.17(p) to cover the fee associated with an information disclosure statement under 37 CFR §1.97(c) in the amount of \$180.00.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

Respectfully submitted,

Date

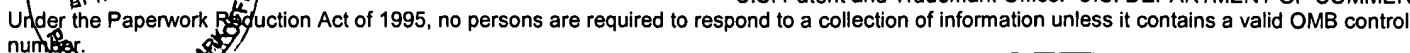
April 14, 2008

FOLEY & LARDNER LLP  
Customer Number: 38706  
Telephone: (650) 251-1129  
Facsimile: (650) 856-3710

By

Antoinette F. Konski

Antoinette F. Konski  
Attorney for Applicant  
Registration No. 34,202



Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449B/PTO

Date Submitted: April 13, 2006

*(use as many sheets as necessary)*

Sheet	1	of	9
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**Complete if Known**

<b>Application Number</b>	09/782,721
<b>Filing Date</b>	2/12/2001
<b>First Named Inventor</b>	H. Michael Shepard
Group Art Unit	1623
Examiner Name	Crane, Lawrence E.
Attorney Docket Number	NB 2004.02 (060925-0402)

[illegible]

Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Application Document		Name of Patentee or Applicant of Cited Document	Filing Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Serial Number	Kind Code <sup>2</sup> (if known)			
	7	2002/0022001	A1	Klecker et al.	02-21-2002	
	8	2002/0034473	A1	Klecker et al.	03-21-2002	
	9	2002/0119094	A1	Klecker et al.	08-29-2002	
	10	2002/0165199	A1	Klecker et al.	11-07-2002	
	11	2003/0049201	A1	Klecker et al.	03-13-2003	
	12	2003/0095921	A1	Klecker et al.	05-22-2003	

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		Office <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
	13	EP	0 095 294	A1	Beecham Group PLC	11-30-1983		
	14	EP	0 283 065	A1	Stichting REGA VZW	09-21-1988		
	15	RO	88451		Antibiotics Enperprise, Inc.	01-30-1986		✓
	16	WO	89/05817		Nucleic Acid Research Institute	06-29-1989		
	17	WO	92/20344		Glaxo Group Ltd.	11-26-1992		
	18	WO	95/01806		Kondratyev, A.	01-19-1995		
	19	WO	95/09865		Terrapin Technologies, Inc.	04-13-1995		
	20	WO	95/12678		Campaign Technology Limited	05-11-1995		
	21	WO	96/33168		Kumiai Chemical Industry Co. Ltd. et al.	10-24-1996		
	22	WO	99/06072		Boehringer Mannheim Corporation	02-11-1999		
	23	WO	99/08110		NewBiotics, Inc.	02-18-1999		
	24	WO	99/37753		NewBiotics, Inc.	07-29-1999		
	25	WO	00/33888		Coulter Pharmaceutical, Inc.	06-15-2000		

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	26	ASCHELE et al. "Immunohistochemical quantitation of thymidylate synthase expression in colorectal cancer metastases predicts for clinical outcome to fluorouracil-based chemotherapy" <i>J. Clin. Oncol.</i> (June 1999) <b>17(6):1760-1770</b>		
	27	BAGSHAW, K.D. "Antibody-directed enzyme prodrug therapy: A review" <i>Drug Development Res.</i> (1995) <b>34(2):220-230</b>		
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	29	BALZARINI et al. "The cytostatic activity of 5-(1-azidovinyl)-2'-deoxyuridine (AzVDU) against herpes simplex virus thymidine kinase gene-transfected FM3A cells is due to inhibition of thymidylate synthase and enhanced by UV light ( $\lambda = 254$ nm) exposure" <i>FEBS Lett.</i> (1995) <b>373:41-44</b>		

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		Group Art Unit	1623
		Examiner Name	Crane, Lawrence E.
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	30	BALZARINI et al. "Mechanism of anti-HIV action of masked alaninyl d4T-MP derivatives" <i>PNAS USA</i> (July 1996) <b>93</b> :7295-7299	
	31	BARBATO et al. "Synthesis of bridged pyrimidine nucleosides and triazo [4, 3-c] pyrimidine nucleoside analogues" <i>Nucleosides &amp; Nucleotides</i> (1989) <b>8</b> (4):515-528	
	32	BARBATO, et al. "Synthesis of bridged pyrimidine nucleosides and triazo [4,3-c] pyrimidine nucleoside analogues" <i>Nucleos. Nucleot.</i> (1991) <b>10</b> (4):853-866	
	33	BATHE et al. "Increased thymidylate synthase gene expression in liver metastases from colorectal carcinoma: implications for chemotherapeutic options and survival" <i>Cancer J. Sci. Am.</i> (1999) <b>5</b> (1):34-40	
	34	BIBLE et al. "Cytotoxic synergy between flavopiridol (NSC 649890, L86-8275) and various antineoplastic agents: the importance of sequence of administration" <i>Cancer Res.</i> (August 15, 1997) <b>57</b> (16):3375-80	
	35	BLACKLEDGE "New developments in cancer treatment with the novel thymidylate synthase inhibitor raltitrexed ('Tomudex')" <i>British J. Cancer</i> (1998) <b>77</b> (Supp 2):29-37	
	36	CASS et al. "Recent advances in the molecular biology of nucleoside transporters of mammalian cells" <i>Biochem. Cell Biol.</i> (1998) <b>76</b> (5):761-770	
	37	CATUCCI et al. "Development and significance of the HIV-1 reverse transcriptase M184V mutation during combination therapy with lamivudine, zidovudine, and protease inhibitors" <i>J. Acquir. Immune Defic. Syndr.</i> (1999) <b>21</b> :203-208	
	38	CHOU and TALALAY, "Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors" <i>Adv. Enzyme Regul.</i> (1984) <b>22</b> :27-55	
	39	CORDON-CARDO and PRIVES "At the crossroads of inflammation and tumorigenesis" <i>J. Exp. Med.</i> (November 15, 1999) <b>190</b> (10):1367-1370	
	40	COSTI et al. "Phthalein derivatives as a new tool for selectivity in thymidylate synthase inhibition" <i>J. Med. Chem.</i> (1999) <b>42</b> (12):2112-2124	
	41	CRUICKSHANK et al. "Oligonucleotide labeling: A concise synthesis of a modified thymidine phosphoramidite" <i>Tetrahedron Lett.</i> (1988) <b>29</b> (41):5221-5224	
	42	CURT "Cancer drug development: new targets for cancer treatment" <i>Oncologist</i> (1996) <b>1</b> (3):II-III	

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	43	CURTIN et al. "Mechanism of Cell Death following Thymidylate Synthase Inhibition: 2'-Deoxyuridine-5'-triphosphate Accumulation, DNA Damage, and Growth Inhibition following Exposure to CB3717 and Dipyridamole" <i>Cancer Res.</i> (May 1, 1991) <b>51</b> :2346-2352		
	44	DeCLERCQ et al. "Antiviral Activity of Novel Deoxyuridine Derivatives" <i>Current Chemotherapy: Proceedings of the International Congress of Chemotherapy</i> (September 18, 1978) <b>1</b> :352-354		
	45	DeCLERCQ "Antiviral Activity Spectrum and Target of Action of Different Classes of Nucleoside Analogues" <i>Nucleosides &amp; Nucleosides</i> (1994) <b>13(6&amp;7)</b> :1271-1295		
	46	DeCLERCQ "In search of a selective antiviral chemotherapy" <i>Clin. Micro. Review</i> (October 1997) <b>10(4)</b> :674-693		
	47	DOLNICK et al. "rTS Gene Expression is Associated with Altered Cell Sensitivity to Thymidylate Synthase Inhibitors" <i>Adv. Enzyme Reg.</i> (1996) <b>36</b> :165-180		
	48	DRAKE et al. "Resistance to Tomudex (ZD1694): Multifactorial in Human Breast and Colon Carcinoma Cell Lines" <i>Biochem. Pharmacol.</i> (1996) <b>51(10)</b> :1349-1355		
	49	EDLER et al. "Immunohistochemically detected thymidylate synthase in colorectal cancer: An independent prognostic factor of survival" <i>Clinical Cancer Research</i> (February 2000) <b>6</b> :488-492		
	50	FARROW et al. "Synthesis and biological properties of novel phosphotriesters: A new approach to the introduction of biologically active nucleotides into cells" <i>J. Med. Chem.</i> (1990) <b>33(5)</b> :1400-1406		
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	52	FREEMANTLE et al. "Molecular characterisation of two cell lines selected for resistance to the folate-based thymidylate synthase inhibitor, ZD1694" <i>British Journal of Cancer</i> (1995) <b>71</b> :925-930		
	53	GOEL et al. "Selective Intraperitoneal Biochemical Modulation of Methotrexate by Dipyridamole" <i>J. Clin. Oncol.</i> (February 1989) <b>7(2)</b> :262-269		
	54	GORLICK et al. "Drug Resistance in Colon Cancer" <i>Semin. Oncol.</i> (December 1999) <b>26(6)</b> :606-611		

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	55	GREM "Biochemical modulation of fluorouracil by dipyridamole: preclinical and clinical experience" <i>Semin Oncol.</i> (April 1992) <b>19(2 Suppl 3):56-65</b>	
	56	GRIENGL et al. "Phosphonoformate and phosphonoacetate derivatives of 5-substituted 2'deoxyuridines: Synthesis and antiviral activity" <i>J. Med. Chem.</i> (1988) <b>31(9):1831-1839</b>	
	57	GRIFFITH et al. "Differential Inhibition of Nucleoside Transport Systems in Mammalian Cells by a New Series of Compounds Related to Lidoflazine and Mioflazine" <i>Biochem. Pharmacol.</i> (1990) <b>40(10):2297-2303</b>	
	58	HAN et al. "Dominant-negative p53 mutations in rheumatoid arthritis" <i>Arthritis Rheum</i> (1999) <b>42(6):1088-92</b>	
	59	HEIDELBERGER et al. "Fluorinated pyrimidines and their nucleosides" <i>Adv. Enzymol. Related Areas Mol. Biol.</i> (1983) <b>54:57-119</b>	
	60	HÓLY et al. "Structure-Antiviral Activity Relationship in the Series of Pyrimidine and Purine N-[2-(2-Phosphonomethoxy)ethyl] Nucleotide Analogues. 1. Derivatives Substituted at the Carbon Atoms of the Base" <i>J. Med. Chem.</i> (1999) <b>42(12):2064-2086</b>	
	61	HOWELL et al. "Comparison of the Synergistic Potentiation of Etoposide, Doxorubicin, and Vinblastine Cytotoxicity by Dipyridamole" <i>Cancer Res.</i> (June 15, 1989) <b>49:3178-3183</b>	
	62	HU et al. "Determination of absorption characteristics of AG337, a novel thymidylate synthase inhibitor, using a perfused rat intestinal model" <i>J. Pharmaceutical Sciences</i> (July 1998) <b>87(7):886-890</b>	
	63	HUSAIN et al. "Elevation of topoisomerase I messenger RNA, protein, and catalytic activity in human tumors: Demonstration of tumor-type specificity and implications for cancer chemotherapy" <i>Cancer Research</i> (January 15, 1994) <b>54:539-546</b>	
	64	JACKMAN "Folate-based thymidylate synthase inhibitors as anticancer drugs" <i>Ann. Oncol.</i> (1995) <b>6(9):871-881</b>	
	65	JOHNSTON et al. "Thymidylate synthase gene and protein expression correlate and are associated with response to 5-fluorouracil in human colorectal and gastric tumors" <i>Cancer Res.</i> (1995) <b>55:1407-1412</b>	
	66	JONES and MANN "New methods of synthesis of $\beta$ -aminoethylpyrazoles" <i>J. Am. Cancer Soc.</i> (1953) <b>75:4048-4052</b>	

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				Filing Date	2/12/2001
				First Named Inventor	H. Michael Shepard
				Group Art Unit	1623
				Examiner Name	Crane, Lawrence E.
Sheet	7	of	9	Attorney Docket Number	NB 2004.02 (060925-0402)

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